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10/533,115

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Yoshiko Takayama

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EXAMINER

WANG, CHANG YU

ART UNIT

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1649

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/533,115

Applicant(s)

TAKAYAMA ET AL.

Examiner

Chang-Yu Wang

Art Unit

1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 April 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 4/29/05, 7/20/05, 8/28/06, 3/9/07.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION
Sequence Rules

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821 through 1.825 because 37CFR 1.821 (a)(2)(c-d) states that each sequence disclosed must appear separately in the "sequence listing" and in the text of the description and claims whenever described. However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, Applicant needs to provide a computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For example, pages 4 and 7 need to be amended to indicate what SEQ ID NOs are represented in formula I and formula XI. See MPEP 2422.04 & 2431.

Note that failure to respond to the requirement for sequence compliance will be held as nonresponsive, and may result in abandonment of this application. Note further

that a new CRF, paper copy and appropriate statement that these are the same and no new mater exists is still required.

Status of Application

2. Claims 1-12 are canceled. Claims 13-16 are pending and under examination in this office action.

Priority

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Specification

4. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Content of Specification

- (a) Title of the Invention: See 37 CFR 1.72(a) and MPEP § 606. The title of the invention should be placed at the top of the first page of the specification unless the title is provided in an application data sheet. The

title of the invention should be brief but technically accurate and descriptive, preferably from two to seven words may not contain more than 500 characters.

- (b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.
- (c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.
- (d) The Names Of The Parties To A Joint Research Agreement: See 37 CFR 1.71(g).
- (e) Incorporation-By-Reference Of Material Submitted On a Compact Disc: The specification is required to include an incorporation-by-reference of electronic documents that are to become part of the permanent United States Patent and Trademark Office records in the file of a patent application. See 37 CFR 1.52(e) and MPEP § 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text were permitted as electronic documents on compact discs beginning on September 8, 2000.
- (f) Background of the Invention: See MPEP § 608.01(c). The specification should set forth the Background of the Invention in two parts:
 - (1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."
 - (2) Description of the Related Art including information disclosed under 37 CFR 1.97 and 37 CFR 1.98: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."
- (g) Brief Summary of the Invention: See MPEP § 608.01(d). A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the

Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

- (h) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.
- (i) Detailed Description of the Invention: See MPEP § 608.01(g). A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.
- (j) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet or electronic page (37 CFR 1.52(b)(3)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps. See 37 CFR 1.75 and MPEP § 608.01(i)-(p).
- (k) Abstract of the Disclosure: See MPEP § 608.01(f). A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims. In an international application which has entered the national stage (37 CFR 1.491(b)), the applicant need not submit an abstract commencing on a separate sheet if an abstract was published with the international application under PCT Article 21. The abstract that appears on the cover page of the pamphlet published by the International Bureau (IB) of the World Intellectual Property Organization (WIPO) is the abstract that will be used by the USPTO. See MPEP § 1893.03(e).
- (l) Sequence Listing. See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed

in a given application, whether the sequences are claimed or not. See MPEP § 2421.02.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

6. Claims 13-16 are objected to because of the following informalities: the recitation "a case" in the claims is not a commonly use for a patient or a subject that needs treatment by administration of an agonist. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting axonal extension of trigeminal nerve cells and recovering corneal sensitivity caused by corneal nerve damage by somatostatin, an somatostatin receptor SSTR2 specific agonist, t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo- 2,3-dihydrobenzoimidazol-1-yl)piperidine-1-carbonyl)amino)propionylamino)hexanoate (compound 1), and an somatostatin receptor SSTR4 specific agonist, 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea (compound 2),

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does not reasonably provide enablement for promoting extension of corneal nerve axon, recovering all forms of corneal sensitivity, treating dry eye and treating all forms of corneal epithelium defect by all somatostatin receptor agonists as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

“There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is ‘undue’. These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)”. See MPEP § 2164.01.

Claims 13-16 are directed to methods of promoting extension of corneal nerve axon, recovering corneal sensitivity, treating dry eye and treating a corneal epithelium defect by a somatostatin receptor agonist.

The instant invention is based on observations on promoting axonal extension of trigeminal nerve cells in cultures by somatostatin, a somatostatin receptor SSTR2 specific agonist and a somatostatin receptor SSTR4 specific agonist. Applicant describes enhanced axonal extension in rabbit trigeminal nerve cells treated with

somatostatin, a somatostatin receptor SSTR2 specific agonist, t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)piperidine-1-carbonyl)amino)propionylamino)hexanoate (compound 1), and a somatostatin receptor SSTR4 specific agonist, 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea (compound 2). Applicant also shows that corneal sensitivity caused by corneal nerve cutting in rabbit can be improved by administration of somatostatin.

Based on the specification and the prior art, Applicant is enabled for promoting axonal extension of trigeminal nerve cells by somatostatin, an somatostatin receptor SSTR2 specific agonist, t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)piperidine-1-carbonyl)amino)propionylamino)hexanoate (compound 1), and an somatostatin receptor SSTR4 specific agonist, 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea (compound 2). Applicant is also enabled for improving corneal sensitivity caused by corneal nerve damage. However, the claims are not limited to the agents and corneal nerves as set forth above. The specification provides insufficient guidance as to enable the claimed invention commensurate in scope with the claims in that only limited somatostatin receptor agonists have been shown to be used in the claimed method and because claims 14 and 16 have not defined what specific diseases are and can be treated by somatostatin receptor agonists.

With regard to the recitation of somatostatin receptor agonist to be used in the claimed methods, Applicant fails to provide sufficient guidance as to enable one of skill

in the art to practice the invention in its full scope because claims 13-16 are single means claims in that they recite "somatostatin receptor agonist". Although Applicants describes several possibilities of somatostatin receptor agonist (see p.11-12), the instant specification defines somatostatin receptor agonists as

"The somatostatin receptor agonist is meant somatostatin per se, as well as those that act on somatostatin receptor and show an action similar to that of somatostatin, and encompasses those referred to as somatostatin agonist, somatostatin analogous form, somatostatin analog and the like." (see p.11)

The definition of somatostatin receptor agonist in the specification encompasses almost any agent, including those yet to be discovered. MPEP 2164.08(a) defines a single means claim as a claim which covered every conceivable means for achieving the stated purpose when the specification disclosed at most only those means known to the inventor. This type of claim was held to be nonenabling for the scope of the claim in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) because the specification disclosed at most only those means known to the inventor. When claims depend on a recited property (i.e. somatostatin receptor agonist), a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See MPEP 2164.08(a). This appears to be the instant case and the claims are not commensurate in scope with the specification.

Based on the specification, Applicant is enabled for using somatostatin, compound 1 and 2 as described in the specification (i.e agonists of SSTR2 and SSTR4) for promoting axonal extension of corneal nerve axon and for improving corneal sensitivity caused by corneal nerve damage. However, Applicant is not enabled for the

claimed invention in its full scope because not all somatostatin receptor agonists can be used in the claimed methods. It is known in the art that the family of somatostatin receptor includes SSTR1-5 and only SSTR2 and SSTR4 are predominantly expressed in the eye (see p. 185, abstract, Mori et al., *Neurosci. Letters*. 1997. 223: 185-188, as in IDS), suggesting that SSTR agonists not specific for SSTR2 and SSTR4 may not have any effect on eye. Thereby, it is unpredictable whether other somatostatin receptor agonists including somatostatin analogs and agonists for SSTR other than SSTR2 and SSTR4 could be used in the claimed method since an amino acid modification on a molecule could abolish the activity of the molecule and other SSTRs are not expressed in the eye.

Applicant describes somatostatin receptor agonists including those acting on somatostatin receptor and showing an action similar to that of somatostatin, and encompassing those referred to as somatostatin agonist, somatostatin analogous form, somatostatin analog (see p.11-12). However, Applicant fails to provide sufficient guidance as to whether all somatostatin receptor agonists including all the modifications on somatostatin or analogs and small molecules for all SSTRs could be used in the claimed method since a single amino acid change could abolish the binding ability of a molecule. For example, a substitution of lysine residue by glutamic acid at position 118 of acidic fibroblast growth factor results in a substantial loss of its biological activity including the binding ability to heparin and its receptor (Burgess et al. *J of Cell Bio.* 111:2129-2138, 1990). Although many amino acid substitutions are possible in any given protein, the position of where such amino acid substitutions can be made is

critical for maintaining the function of a protein; i.e. only certain positions can tolerate conservative substitutions without changing the relationship of three dimensional structure and function of the protein (col 2, p. 1306, Bowie et al. Science, 1990, 247:1306-1310). Although the specification outlines art-recognized procedures for producing and the screening method, this is not adequate guidance as to the nature of active somatostatin receptor agonists that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would not immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active because conformation is dependent upon surrounding residues; i.e. substitution of non-essential residues can often destroy activity. In addition to a core determinant sequence, the protein-protein interaction also relies on the flanking or noncontiguous residues (see p. 445 the second column, first paragraph, Pawson et al. 2003, Science 300:445-452). The optimal binding motif for a domain is not necessarily suitable for physiological or in vivo interaction. The predictive data always need to be validated by actual analyses in cells (see p. 445, 3rd col., 2nd paragraph, Pawson et al. 2003, Science 300:445-452). Applicant fails to teach what other structures/amino acid sequences could/could not be included/changed in all somatostatin receptor agonists in order to preserve the activity of somatostatin in promoting axonal extension of corneal nerves or treating dry eye or all corneal epithelium defects. Applicant fails to provide sufficient guidance as to what other structures/characteristics are required for the small molecules

of somatostatin agonists in order to maintain the activity of somatostatin in enhancing axonal extension or even in treating all corneal epithelium defects.

In addition, based on the specification and the prior art, Applicant is enabled for enhancing axonal extension of corneal nerves and improving corneal sensitivity caused by corneal nerve damage by administration of somatostatin and compounds 1 and 2.

However, Applicant fails to provide sufficient guidance as to enable one of skill in the art to practice the full scope of the invention without undue experimentation since neither the specification nor the prior art teaches that administration of a somatostatin receptor agonist could recover all forms of corneal sensitivity caused by all possible mechanisms or treat all forms of corneal epithelium defect. It is known in the art that corneal

epithelium defect can be characterized as chronic persistent, advanced or permanent.

The causes of different forms of corneal sensitivity and corneal epithelium defects are different. For example, corneal epithelium defect could be due to infection, surgery or due to genetic mutations of genes involved in corneal epithelium development such as sonic hedgehog (see p. 577 abstract; Saika et al. Invest. Ophthal. Vis. Sci. 2004.

45:2577-2585). If a corneal epithelium defect is due to deficiency of sonic hedgehog, it is unpredictable whether administration of somatostatin or other agonists can be used to treat this type of corneal epithelium defect since sonic hedgehog is essential for corneal epithelium development. Applicant fails to teach what constitutes in the recitation of corneal sensitivity and in the recitation of corneal epithelium defect. Applicant fails to provide sufficient guidance as to what specific diseases may be caused by a specific corneal epithelium defect with a specific mechanism and can be improved by

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administration of somatostatin or other somatostatin receptor agonists. Thus, it is unpredictable whether somatostatin or other somatostatin agonists can be used to treat these undefined corneal epithelium defects or undefined corneal sensitivity. Since the claims 14 and 16 fail to define what diseases are and what diseases can be treated, a skilled artisan cannot contemplate what types of corneal epithelium defect can be improved by administration of somatostatin receptor agonists and within the scope of the claims. Therefore, in view of the breadth of the claims, the lack of guidance in the specification, the unpredictability of inventions, and current status of the prior art, undue experimentation would be required to a person of skill in the art to practice the claimed invention as it pertains to methods of promoting extension of corneal nerve axon, recovering corneal sensitivity, treating dry eye and treating a corneal epithelium defect by a somatostatin receptor agonist.

8. Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 13-16 are drawn to methods of promoting extension of corneal nerve axon, recovering corneal sensitivity, treating dry eye and treating a corneal epithelium defect by a somatostatin receptor agonist. The claims encompass a genus of somatostatin receptor agonists to be used in the claimed methods. Claim 15 encompasses a genus of corneal sensitivity caused by all possible mechanisms. Claim 16 also encompasses a genus of corneal epithelium defect caused by all possible mechanisms. Applicant has not disclosed sufficient species for the broad genus of somatostatin receptor agonists to be used in the method of promoting extension of corneal nerve axon. Applicant also fails to disclose sufficient species for the broad genus of corneal epithelium defect to be treated or corneal sensitivity to be recovered by a somatostatin receptor agonist. The specification only describes somatostatin, a somatostatin receptor SSTR2 specific agonist, t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)piperidine-1-carbonyl)amino)propionylamino)hexanoate (compound 1), and a somatostatin receptor SSTR4 specific agonist, 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea (compound 2) to be used in the claimed method of promoting axonal extension and of improving corneal sensitivity caused by corneal nerve cutting (p.20-21). However, the claims are not limited to the somatostatin receptor agonists as set forth above and are not limited to promoting axonal extension of corneal nerves.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is in possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of somatostatin, a somatostatin receptor SSTR2 specific agonist, t-butyl 6-amino-2-(3-(1H-indol-3-yl)-2-((4-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)piperidine-1-carbonyl)amino)propionylamino)hexanoate (compound 1), and a somatostatin receptor SSTR4 specific agonist, 1-(3-(N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino)propyl)-3-(3-(1H-imidazol-4-yl)propyl)thiourea (compound 2) in promoting axonal extension of corneal nerves and recovering corneal sensitivity caused by corneal nerve damage. Although Applicant describes several different somatostatin receptor agonists, Applicant is not in possession of other somatostatin receptor agonists described in the specification in promoting axonal extension of corneal nerves and treating all forms of corneal epithelium defect and all forms of corneal sensitivity. Applicant is not in possession of methods of treating all forms of corneal epithelium defect and all forms of corneal sensitivity. The instant specification fails to provide sufficient descriptive information, such as definitive structural of the claimed genus of somatostatin receptor agonists including somatostatin analogs to be used in promoting axonal extension of corneal nerves. There is no description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure of small molecules or other somatostatin receptor agonists to somatostatin function.

Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify other somatostatin receptor agonists and what other somatostatin receptor agonists might be and to be used in the claimed method. Since the common characteristics/features of other somatostatin receptor agonists that can be used in the claimed methods are unknown, a skilled artisan cannot envision the functional correlations of the genus with the claimed invention. In addition, neither the specification nor the prior art provides sufficient description to reasonably demonstrate Applicant's possession of the claimed method of treating all forms of corneal epithelium defect and all forms of corneal sensitivity by any somatostatin receptor agonist.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the methods of promoting extension of corneal nerve axon, recovering corneal sensitivity, treating dry eye and treating a corneal epithelium defect by a somatostatin receptor agonist have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1.115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. See MPEP § 2163.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-16 are rejected under 35 U.S.C. 102 (b) as being anticipated by Nordisk (WO98/58646, published on Dec 30, 1998 as in IDS).

Nordisk (WO'646) teaches a method of treating several eye diseases including glaucoma, inflammation of corneal stroma, stromal keratitis, iritis, retinitis, cataract and conjunctivitis by somatostatin (i.e. as it relates to claims 13-16; see abstract; p.3, p.5; p.9-23 for somatostatin receptor agonists). Since the patient population, the affected area (i.e. eye) and the material (somatostatin receptor agonists) used in the method of Nordisk (WO'646) are identical to the instant claimed methods as recited in claims 13-16, the limitation of promoting axonal extension in claim 13, the limitation of recovering corneal sensitivity in claim 14 and the limitation of treating dry eye in claim 15 are inherent results of administration of somatostatin in these diseases because these diseases would cause dry eye and corneal sensitivity; and the structure of cornea is within the eye and eye contains conjunctiva, cornea, iris, retina and optic nerve (see p.2 of the data retrieved from the NEI website, www.nei.nih.gov/health/cornealdisease). Thus, the effects of somatostatin receptor agonists on axonal extension, recovering corneal sensitivity and dry eye would inherently occur upon administration of somatostatin receptor agonists into the eye. In addition, conjunctivitis, inflammation of corneal stroma, stromal keratitis also result in corneal epithelium defect as evidenced by Suzuki et al. (see p. 550, abstract, Suzuki et al. Curr Eye Res. 2000. 21:550-553) and Fini et al. (see p. S12 2nd col., Fini et al. Arch Dermatol. Res. 1998. 290: S12-S23) since these diseases also affect corneal epithelium. Particularly, conjunctivitis, inflammation of corneal stroma and stromal keratitis (herpes virus infection on cornea) would also cause

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corneal epithelium defect because these illness would affect cornea and the cornea encompasses five layers of cells including epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium (from outside to inside of the cornea; see p.3-4 of the data retrieved from the NEI website, www.nei.nih.gov/health/cornealdisease). Suzuki et al. teach that conjunctival inflammation (conjunctivitis) induces migration of Langerhans cells to corneal to attach corneal epithelium and consequently affect corneal allografts (see p. 550, abstract). Fini et al. teach that corneal ulceration can be caused by stromal keratitis (herpes virus infection on cornea) and stromal ulceration is initiated by defective healing of corneal epithelium (see p.S13, 2nd col & table 1). Thus, the treatment of conjunctivitis, inflammation of corneal stroma, stromal keratitis by somatostatin as disclosed by Nordisk (WO'646) would inherently treat corneal epithelium defect as recited in claim 16. Since the materials (somatostatin receptor agonists), affected tissue and area within the patients suffering from eye diseases are the same between the claimed method and the method of Nordisk (WO'646), the administration of somatostatin receptor agonists to the eye would inherently have the effects on the entire eye structures including corneal nerve axon and corneal epithelium. Thus, claims 13-16 are anticipated by Nordisk (WO98/58646).

Conclusion

11. NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

US6127343 teaches a somatostatin agonist to treat glaucoma.

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/

Chang-Yu Wang, Ph.D.
September 14, 2007

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud